Cost-effectiveness of carfilzomib *(*Kyprolis®*)* (in combination with lenalidomide and dexamethasone) for the treatment of adult patients with multiple myeloma who have received at least one prior therapy

The NCPE has issued a recommendation regarding the cost-effectiveness of carfilzomib (Kyprolis®). Following NCPE assessment of the applicant's submission, carfilzomib (Kyprolis®) (in combination with lenalidomide and dexamethasone) is not considered cost-effective for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the applicant's (Amgen) economic dossier on the cost effectiveness of carfilzomib. The NCPE uses a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health related quality of life benefits that the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examine all the evidence that may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **19.10.2016**

Summary

In March 2016, Amgen submitted a dossier examining the cost-effectiveness of carfilzomib *(Kyprolis®)* (CAR) in combination with lenalidomide (LEN) and dexamethasone (DEX) for the treatment of adult patients with multiple myeloma (MM) who have received at least one prior therapy. On 26th May 2016 the EMA added a licence extension to the marketing authorisation for CAR adding that CAR in combination with either LEN + DEX or DEX alone is indicated for the treatment of adults patients with MM who have received at least one prior therapy. The cost-effectiveness of CAR in combination with DEX alone was not investigated in this submission.

1. Comparative Effectiveness

- Currently bortezomib (BOR) (as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone (DEX)) and lenalidomide (LEN) + DEX are licenced in Ireland as second line therapy for multiple myeloma (MM). In the submission, the main comparator in the base case analysis was LEN+DEX. Carfilzomib (CAR) is administered as a triplet regimen with LEN+DEX and LEN+DEX is the only treatment for which direct comparative evidence is available. A comparison with BOR+LEN+DEX was included as a scenario analysis on advice to the Applicant from Irish clinicians, suggesting that BOR+LEN+DEX (despite being unlicensed) is commonly used in clinical practice in Ireland at first relapse.
- The evidence submitted to support efficacy was based on the ASPIRE study. ASPIRE is a randomised, controlled, open-label, multicentre, phase 3 study that enrolled adult patients with symptomatic relapsed MM and measurable disease who had received one to three prior treatment regimens, had an expected life expectancy of at least 3 months and an ECOG of 0-2. The primary endpoint was progression-free survival (PFS). Secondary efficacy endpoints included overall survival (OS), overall response rate, duration of response, disease control rate, and changes over time in the Global Health Status/Quality of Life subscale of the EORTC QLQ-C30.
- The median PFS was 26.3 months (95% CI 23.3, 30.5) for CAR+LEN+DEX versus 17.6 months (95% CI 15.0, 20.6) for LEN+DEX, HR = 0.69 (95% CI 0.57, 0.83). Median OS was not reached in either of the study arms at the time of data cut-off however patients in the CAR+LEN+DEX arm had a nominally statistically

significant reduction of 21% in the risk of death compared with those in the LEN+DEX arm (36% compared to 41% respectively) (HR 0.79; 95% CI: 0.63, 0.99). The Kaplan-Meier 24-month OS rates were 73.3% (95% CI: 68.6, 77.5) in the CAR+LEN+DEX arm group and 65.0% (95% CI: 59.9, 69.5) in the LEN+DEX arm. It should be noted that patients who progressed were eligible for salvage therapy which may have confounded the OS results. The overall response rate for patients achieving at least a partial response was 87.1% in the CAR+LEN+DEX arm compared with 66.7% in the LEN+DEX arm (OR 3.472; 95% CI 2.41, 5.00). The percentage of patients who achieved a complete response was 31.8% in the CAR+LEN+DEX arm compared to 9.3% in the LEN+DEX arm. The median time to response was 1 month with a mean of 1.6 months in the CAR+LEN+DEX arm. The median and mean times to response in the LEN+DEX arm were 1 month and 2.3 months, respectively.

- Direct comparative data was not available for the comparison of CAR+LEN+DEX versus BOR+LEN+DEX. To inform this comparison, clinical efficacy for BOR+LEN+DEX was based on the efficacy for CAR+LEN+DEX observed in the ASPIRE study, adjusted for differences between CAR and BOR observed in the ENDEAVOR study, which compared CAR+DEX with BOR+DEX. In the absence of direct head-to-head data the NCPE considers this approach to be reasonable. The NCPE however has some concerns that the assumptions of duration of treatment effect and background LEN+DEX treatment were not applied consistently across the two treatment arms in the economic model. The NCPE also has concerns that the dose of CAR used in the ENDEAVOR study was twice as high as that used in the ASPIRE study.

2. Safety

- Treatment-related adverse events occurring more frequently in the CAR+LEN+DEX arm included neutropenia, thrombocytopenia, pneumonia and hypophosphatemia. Cardiac failure adverse events were also increased in the CAR+LEN+DEX arm (6.4% all grades, 3.8% ≥ Grade 3) compared with the LEN+DEX arm (4.1% all grades, 1.8% ≥ Grade 3). The CHMP has previously endorsed a risk management plan which identifies cardiac toxicity as an important risk with the use of CAR.
- A total of 142 patients (36.2%) in the CAR+LEN+DEX arm, and 160 patients (41.1%) in the LEN+DEX arm had died at the time of data cut-off. The most common cause of death was disease progression.

3. Cost-Effectiveness analysis

- Cost utility analyses comparing CAR+LEN+DEX with LEN+DEX and BOR+LEN+DEX were submitted by the company. The perspective of the HSE (payer) was presented.
- The model was a multi-state cost-utility Markov model, incorporating three health states: progression-free, progressed disease and death.
- The time horizon was 40-years (reflecting a life-time horizon), with 28-day cycles.
- Health benefit was measured in quality adjusted life years (QALYs). Utility values for the progression-free state were predicted by mapping health related quality of life data collected in the ASPIRE study using published algorithms. Utility estimates for the progressed disease state were obtained from a cost utility analysis comparing different chemotherapy regimens in newly diagnosed MM patients. Utilities for BOR+LEN+DEX were assumed to be equivalent to those predicted for CAR+LEN+DEX while patients were actively treated with BOR and were then assumed to revert to those predicted for LEN+DEX patients. The NCPE has concerns that this assumption was not applied to CAR+LEN+DEX. Utility decrements for adverse events were also included in the model. The NCPE has concerns regarding the omission of utility decrements and costs for pneumonia and cardiac failure in the model.
- Costs included drug acquisition and administration, health state costs, monitoring costs and costs associated with end-of-life care and adverse events. The NCPE has some concerns regarding the capping of costs associated with CAR at 18 cycles in line with the treatment duration in the ASPIRE study when the marketing authority allows for continued CAR treatment after this time. The NCPE also has several concerns regarding the assumptions of duration of treatment effect for CAR+LEN+DEX applied in the model, especially in regard to the assumption that treatment effect of CAR+LEN+DEX persists for the entire duration of the model.
- The main efficacy outcomes used in the model were PFS and OS, based on multivariate parametric survival curves fitted to data from the ASPIRE study. The difference in area between the OS and PFS curves indicates the proportion of patients in the progressed disease state.

Results

- The incremental cost due to treatment with CAR+LEN+DEX versus LEN+DEX was €107,801 for a QALY gain of 0.86 resulting in an ICER of €125,759 per QALY.
- The incremental cost due to treatment with CAR+LEN+DEX versus BOR+LEN+DEX was €59,175 for a QALY gain of 0.81 resulting in an ICER of €73,449 per QALY.

Sensitivity analysis

- One way sensitivity analyses were performed with model input parameters varied across their plausible ranges. These analyses showed that for both the CAR+LEN+DEX versus LEN+DEX and the CAR+LEN+DEX versus BOR+LEN+DEX comparisons the model is most sensitive to those parameters associated with the extrapolation of OS, utility values, time to discontinuation of LEN and the treatment effect covariate for PFS. The model was also sensitive to several other parameters associated with PFS in the CAR+LEN+DEX versus BOR+LEN+DEX comparison.
- Several scenario analyses were also performed. The cost utility results were most sensitive to: assumptions regarding duration of treatment effect, assumptions regarding duration of CAR treatment and inclusion of drug wastage. All of which increased the ICER. Excluding the additional costs of LEN+DEX in the CAR+LEN+DEX treatment arm incurred by increased PFS decreased the ICER.
- The probability of cost effectiveness at a threshold of €45,000/QALY was estimated at 0% for the CAR+LEN+DEX versus LEN+DEX comparison.
- The probability of cost effectiveness at a threshold of €45,000/QALY was estimated at 4.3% for the CAR+LEN+DEX versus BOR+LEN+DEX comparison.

4. Budget Impact Analysis

The company estimate that approximately 151 new patients would be eligible for treatment annually and predict market share of 6.31% in Year 1, increasing to 25% in Year 5.

The price to wholesaler of CAR is €1,247 for the 60mg vial and the annual cost of treatment per patient is approximately €105,721

The projected gross drug budget impact (including acquisition cost of CAR) based on company estimates of market share, is; €835,360 (year 1), €3,310,623 (year 2), €5,651,429 (year 3), €8,370,857 (year 4) and €9,059,374 (year 5). Therefore, the gross cumulative 5 year budget impact of CAR is approximately €26.4 million.

The cumulative net budget impact of the introduction of CAR over 5 years is approximately €9,690,581.

5. Conclusion

Following review of the company submission, carfilzomib (Kyprolis®) (in combination with lenalidomide and dexamethasone) is not considered to be cost-effective for the treatment of adult patients with multiple myeloma who have received at least one prior therapy, at a threshold of €45,000/QALY.